REMARKS

Claims 1-15, 21, 29-30, and 55-64 are pending. Claims 31-36 and 43-54 were previously withdrawn from consideration and are now canceled. Claims 16-20 and 37-42 were previously canceled. Claims 1, 15, 29, and 56-64 are amended. Reconsideration of the application in view of the above amendments and the following remarks is respectfully requested.

I. ELECTION/RESTRICTIONS

The Office indicates that Claims 31-36 and 43-54 were withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12. To complete the reply to the final rejection, Applicant cancels without prejudice Claims 31-36 and 43-54 drawn to the nonelected invention. Thus, Claims 1-15, 21, 29-30, and 55-64 are pending in the application.

II. 35 U.S.C. § 112 CLAIM REJECTION

The Office rejected Claims 1-15 and 29-36 under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for [a] method of modifying activity of hnRNP A proteins, does not reasonably provide enablement for [a] method of modifying activity of any other nucleotide binding proteins." This rejection is respectfully traversed.

Applicant has amended Claims 1-15 to further specify and define an embodiment of the present invention. While the Office states that the specification "...[is] enable[ed] for [a] method of modifying [the] activity of hnRNP A proteins...," the Office rejects

Claims 29 and 30 drawn to "a method of modifying an activity at least one hnRNP A1 protein ... ." Applicant inquires if the rejection of Claims 29 and 30 is a typographical error. Claims 31-36 have been canceled. Claims 1-15 as amended are directed to a method of modifying the activity of hnRNP A proteins. Applicant respectfully requests the withdrawal of this rejection.

III. 35 U.S.C. § 102 CLAIM REJECTIONS

A. CLAIMS 1, 3, 6, 11, 15, 29, AND 30 ARE PATENTABLY DISTINGUISHABLE FROM BLANCHETTE, *ET AL.*

The Office rejected Claims 1, 3, 6, 11, 15, 29, and 30 under 35 U.S.C. § 102(b) as being anticipated by Blanchette, *et al.* This rejection is respectfully traversed.

Blanchette, *et al.* discloses the use of CE1 and CE4 sequences *located upstream and downstream* of the mouse hnRNP A1 exon 7B to control the inclusion of exon 7B in the spliced RNA. Blanchette at 1940. The CE1 and CE4 sequences are *cis*-acting, meaning that the regulatory elements are part of the target RNA sequence. *Id.* This is contrasted with *trans*-elements that are physically unlinked to a target RNA sequence to block the activity of, in this case, an RNA binding protein. Applicants' invention uses introduced *trans*-elements to modify the activity of hnRNP A protein. In particular, a plurality of polynucleotide sequences are *introduced into a cell.* Applicants' Application at 56-57, 66-67. The polynucleotide sequences in Applicants' invention, unlike Blanchette, are not located upstream or downstream of the target RNA sequence(s). Claims 1, 15, and 29 have been amended to reflect the *trans* nature of the polynucleotide sequences. Since Claims 3, 5, 11, and 30 depend from and contain all the limitations of Claims 1 and 29, Claims 3, 5, 11, and 30 also point out and distinctly

claim the subject matter which Applicant regards as an embodiment of the invention in the same manner as Claims 1 and 29. 35 U.S.C. § 112 (1994). Thus, Applicants' invention is patentably distinguishable from Blanchette, *et al.* Applicant respectfully requests the withdrawal of this rejection.

B. CLAIMS 1, 3, 6-8, 10-12, 14, AND 15 ARE PATENTABLY DISTINGUISHABLE FROM MCNALLY, *ET AL.*

The Office rejected Claims 1, 3, 6-8, 10-12, 14, and 15 under 35 U.S.C. § 102(b) as being anticipated by McNally, *et al.* This rejection is respectfully traversed.

McNally, *et al.* studied *cis*-acting elements in the *gag* region, termed the negative regulator of splicing (NRS) that disrupts binding to one or another RNA binding protein. McNally at 2385-86. Because *cis*-elements are regulatory elements found within the target RNA sequence, Applicants' *trans*-acting elements are distinguishable from McNally's *cis*-elements. Claims 1 and 15 have been amended to reflect the *trans* nature of the polynucleotide sequences. Since Claims 3, 6-8, 10-12, and 14 depend from and contain all the limitations of Claims 1 and 15, Claims 3, 6-8, 10-12, and 14 also point out and distinctly claim the subject matter which Applicant regards as an embodiment of the invention in the same manner as Claims 1 and 15. 35 U.S.C. § 112. Thus, Applicants' invention is patentably distinguishable from McNally, *et al.* Applicant respectfully requests the withdrawal of this rejection.

C. CLAIMS 55, 56, AND 61-64 ARE PATENTABLY DISTINGUISHABLE FROM MURO, *ET AL.*

The Office rejected Claims 55, 56, and 61-64 under 35 U.S.C. § 102(b) as being anticipated by Muro, *et al.* This rejection is respectfully traversed.

Muro, *et al.* studied experiments done on the EDA alternative splicing region of the fibronectin primary transcript. Muro, *et al.* at 2657. Muro tested the exonic splicing enhancer (ESE) and exonic splicing silencer (ESS) elements in the EDA region showing that only the ESE element is active in different environments. *Id.* at 2657-58. The ESS and ESE regions are sequences found on the endogenous RNA and thus, are cis-acting. *Id.* at 2657. Muro conducted experiments that alter the secondary structure of the ESS and ESE of EDA. *Id.* at 2658-66. This in turn alters the exposure of the ESS and ESE regions recognized by the *trans*-acting factors. *Id.* at 2657, 2670.

Contrary to Muro, Applicants' are not altering the endogenous sequence of the primary transcript of fibronectin or hnRNP A. Applicants' invention seeks to alter the activity of hnRNP A protein with the addition of a plurality of polynucleotide sequences to the cell that inhibit the binding of hnRNP A to the endogenous RNA sequences. *See* Applicants' Claim 1. In the case of Claims 55, 56 and 61-64, the polynucleotide sequences added to the cell are ESS and ESE sequences. These ESS and ESE sequences added are mimics (competitive antagonists) of the endogenous splicing silences and enhancers. Applicants Application at 66. This addition does not alter or effect the integrity of the endogenous ESE or ESS sequences of EDA like Muro. Thus, Applicants' present invention is patentably distinguishable from Muro, *et al.* Applicant respectfully requests the withdrawal of this rejection.

D. CLAIMS 55, 56, 59, AND 60 ARE PATENTABLY DISTINGUISHABLE FROM HASTINGS.

The Office rejected Claims 55, 56, 59, and 60 under 35 U.S.C. § 102(b) as being anticipated by Hastings, *et al.* This rejection is respectfully traversed.

As in Muro, *et al.*, Hastings, *et al.* examines "the requirements for alternative processing of TRα1 and TRα2 mRNA using a model erbAα minigene." Hastings, *et al.* at 11507. Hastings uses various techniques such as single-nucleotide substitutions and deletions to regulate processing of TRα1 and TRα2. *Id.* at 11509-11. In particular, Hastings hypothesized and tested whether "intronic sequences may regulate TRα2 mRNA processing." *Id.* at 11509, Fig.3. Thus, Hastings like Muro alters the endogenous intronic splicing enhancers (ISE).

Applicants' invention, however, fails to alter or modify the endogenous intronic splicing silencer (ISS) or ISE. As stated previously, Applicants' introduce polynucleotide sequences to cells as mimics (competitive antagonists) of the endogenous splicing silences and enhancers (ESSs, ESEs, ISEs, and/or ISSs). Applicants Application at 66. Unlike Hastings, this addition does not alter or effect the integrity of the endogenous ISE or ISS sequences of TRα1 and TRα2. Thus, Applicants' present invention is patentably distinguishable from Hastings, *et al.* Applicant respectfully requests the withdrawal of this rejection.

IV. 35 U.S.C. § 103 CLAIM REJECTIONS

A. CLAIM 9 IS PATENTABLY DISTINGUISHABLE OVER BLANCHETTE, *ET AL.* IN VIEW OF ROSS, *ET AL.*

The Office rejected Claim 9 under 35 U.S.C. § 103(a) as being unpatentable over Blanchette, *et al.* as applied to Claims 1, 3, 6, 11, 15-18, and 37-42, and further in view of Ross, *et al.* This rejection is respectfully traversed.

Blanchette, *et al.*, as stated *supra*, teaches the use of *cis*-acting polynucleotides to alter the activity of RNA binding proteins. Blanchette at 1940. Unlike Blanchette, Applicants' invention introduces *trans*-acting polynucleotides into the cell to modify the activity of hnRNP A protein. Applicants' Application at 56-57, 66-67. Because Blanchette fails to teach *trans*-acting polynucleotides, the combination of Blanchette and Ross fail to teach all the claim limitations. *See* Manual of Patent Examining Procedure § § 706.02(J), 2142 (8th ed. Rev. 1 2003) (hereinafter "MPEP"). Further, the combination fails to provide a reasonable expectation of success. MPEP § 2143.02. Thus, Applicant's invention is patentably distinguishable over Blanchette, *et al.* in view of Ross, *et al.*

In addition, Claim 9 depends from Claim 1. Because of this dependency, Claim 9 is construed to incorporate all the limitations of Claim 1. *See* 35 U.S.C. § 112. As stated under the Section 102 analysis, Claim 1 is patentably distinguishable from the disclosures in Blanchette, *et al.* and thus, Claim 9 is thought to include all the limitations of Claim 1 and provides that the cells are avian. Blanchette, *et al.* in view of Ross, *et al.* does not teach all the of the limitations and thus, Claim 9 is patentably distinguishable. Applicant respectdully requests the withdrawal of this rejection.

V. CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the claims of the present invention define subject matter patentable over the references cited by the Office and that the application is in condition for allowance. Should the Office believe that anything further is desirable to place the application in better condition for allowance, the Office is invited to contact Applicants' undersigned attorney at the below listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to deposit account number 03-2469. Moreover, if the deposit account contains insufficient funds, the Commissioner is hereby invited to contact Applicant's undersigned representative to arrange payment.

Respectfully submitted,

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JOHN N. COULBY, Reg. No. 43,565
COLLIER SHANNON SCOTT, PLLC
3050 K Street, N.W., Suite 400
Washington, D.C. 20007
(202) 342-8400